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Published in:
Nature Nanotechnology

DOI:
[10.1038/nnano.2006.45](https://doi.org/10.1038/nnano.2006.45)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2006

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Citation for published version (APA):
Browne, W. R., & Feringa, B. L. (2006). Making molecular machines work. *Nature Nanotechnology*, 1(1), 25-35. <https://doi.org/10.1038/nnano.2006.45>

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Making molecular machines work

In this review we chart recent advances in what is at once an old and very new field of endeavour — the achievement of control of motion at the molecular level including solid-state and surface-mounted rotors, and its natural progression to the development of synthetic molecular machines. Besides a discussion of design principles used to control linear and rotary motion in such molecular systems, this review will address the advances towards the construction of synthetic machines that can perform useful functions. Approaches taken by several research groups to construct wholly synthetic molecular machines and devices are compared. This will be illustrated with molecular rotors, elevators, valves, transporters, muscles and other motor functions used to develop smart materials. The demonstration of molecular machinery is highlighted through recent examples of systems capable of effecting macroscopic movement through concerted molecular motion. Several approaches to illustrate how molecular motor systems have been used to accomplish work are discussed. We will conclude with prospects for future developments in this exciting field of nanotechnology.

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Consider a world composed of nanometre-sized factories and self-repairing molecular machines where complex and responsive processes operate under exquisite control; where translational and rotational movement is directed with precision; a nano-world fuelled by chemical and light energy. What images come to mind? The fantastical universes described in the science fiction of Asimov and his contemporaries? To a scientist, perhaps the 'simple' cell springs more easily to mind with its intricate arrangement of organelles and enzymatic systems fuelled by solar energy (as in photosynthetic systems) or by the chemical energy stored in the molecular bonds of nucleotide triphosphates (for example, ATP)¹. Understanding and harnessing such phenomenal biological systems provides a strong incentive to design active nanostructures that can operate as molecular machines², and although our current efforts to control motion at the molecular level may appear awkward compared with these natural systems, it should not be forgotten that nature has had a 4.5 billion year head start.

Biological motors³ convert chemical energy to effect stepwise linear or rotary motion, and are essential in controlling and performing a wide variety of biological functions. Linear motor proteins are central to many biological processes including muscle contraction, intracellular transport and signal transduction, and ATP synthase, a genuine molecular rotary motor, is involved in the synthesis and hydrolysis of ATP^{1,2,4}. Other fascinating examples include membrane translocation proteins, the flagella motor that enables bacterial movement⁵ and proteins that can entrap and release guests through chemomechanical motion^{2,3}. In recent years the development of biomolecular motors (and natural–synthetic hybrid systems) towards the construction of sensors, actuators

and transporters has seen tremendous progress^{6,7}. Biological motors are important components in the fabrication of dynamic smart materials, and semi-synthetic DNA-based structures have been explored in building a variety of mechanical motor-like functions^{8–10}.

Although biological motors are capable of complex and intricate functions, a key disadvantage of their application *ex vivo* arises in their inherent instability and restrictions in the environmental conditions they operate in¹¹. Whereas nature is capable of maintaining and repairing damaged molecular systems, such complex repair mechanisms are beyond the capabilities of current nanotechnology. By contrast, wholly synthetic systems, which can tolerate a more diverse range of conditions than biological machines, offer considerable advantages in the development of complex nanomachinery.

Furthermore the sheer excitement of being able to build completely artificial motors and machines of nanodimensions, in the bottom-up approach promulgated by Feynman¹² several decades ago, has provided the drive to attempt the synthetic challenges that such molecular machines present. A synthetic approach to the construction of molecular devices not only serves to mimic and build on the elegant systems nature has to offer but also can be used to develop systems that are not restricted to nature's small, albeit versatile, synthetic toolbox.

Central to any molecular machine is the motor component and hence it is conceivable that molecular motors and machines (Fig. 1)^{13–23} will play as prominent a role in the nanotechnological revolution of the twenty-first century as their macroscopic counterparts — the steam and internal combustion engines — played in catalysing the industrial revolution of the nineteenth century.

MOLECULAR MOTION

Before surveying various approaches taken towards developing artificial molecular machines, it may be pertinent to first address a

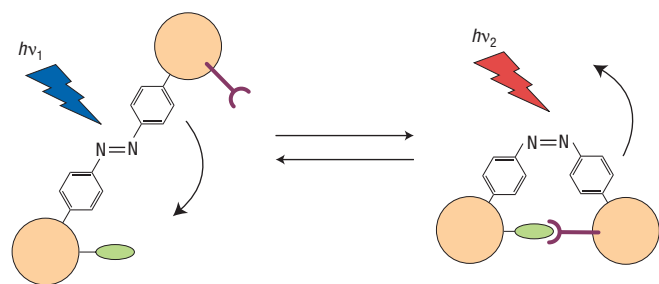


Figure 1 What makes a molecule a machine? In this example of a molecular machine we are able to switch between two molecular states (shapes) in a controlled manner as part of a repetitious mechanical cycle. An azobenzene molecule can exist in two forms (left: *trans* with the bulky groups on opposite sides of the double bond, and right: *cis* with the bulky groups on the same side). The bulky groups can be moved closer together or further apart by switching between the *cis* and *trans* forms (see also, Fig. 8b). This switching can be performed by using light of two different colours, one to go from *cis* to *trans*, the other to reverse the process.

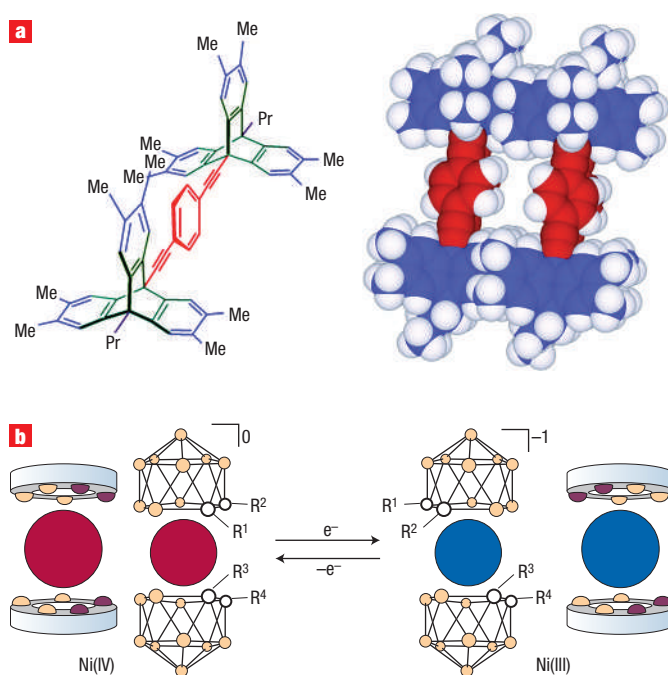


Figure 2 Examples of non-directionally controlled molecular rotors. **a**, A molecular rotor (left) where hindrance to rotation of the central phenyl ring (the rotor) is removed by the upper and lower bulky molecular end units (the stators). Sufficient spacing for the phenyl rings is generated to allow fast rotation in the solid state as illustrated for two rotor units (right). Reproduced with permission from ref. 32. Copyright (2005) National Academy of Sciences, USA. **b**, An electrochemically driven rotor where the upper and lower carborane (polyhedral clusters comprising boron and carbon atoms) moieties are bound as ligands to a nickel ion functioning as a ‘ball-bearing’. Oxidation and reduction of the nickel centre (the $\text{Ni}^{3+}/\text{Ni}^{4+}$ redox cycle) leads to rotation of the upper ligand relative to the lower ligand, changing the relative position of the alkyl groups ($\text{R}^1\text{--}\text{R}^4$) attached to the carborane ligands. Reprinted with permission from ref. 36. Copyright (2004) American Association of the Advancement of Science.

sometimes controversial, if somewhat semantic, aspect of this field of nanotechnology: specifically, what do we mean when we refer to molecules as machines and motors?

At the heart of every machine is its motor. *The Oxford Dictionary of English*²⁴ defines a motor as “a thing that imparts motion”; work as “the operation of a force in producing movement or other physical change”; and motion as “the condition of a body, when at each successive point in time it occupies a different position or orientation in space”. Perhaps, a more utilitarian definition of a motor is a device that converts fuel, be it chemical, thermal or light, into kinetic energy in a controlled manner — that is, it makes things move.

A major difficulty in operating molecular machines, however, lies not in achieving motion at the molecular level but in controlling their operation, especially their directionality. Whereas the most critical design issue facing macroscopic machines is their function, in designing molecular machines making motion ‘visible’ is of paramount importance. It is for this reason that scientists have turned to using ‘reporting’ components in the design and construction of molecular machines and, more often than not, asymmetry is key to the successful demonstration of directionally controlled motion. Indeed asymmetry, as we shall see, is central to directional control in the majority of systems reported to date. In terms of size, however, bigger is not always better. Indeed, smaller molecular systems offer distinct advantages over larger assemblies in terms of synthetic chemistry, characterization and importantly in the ability to fine-tune molecular properties systematically. Finally, to translate molecular movement to macroscopic levels, many molecular motors must be able to work cooperatively.

BROWNIAN ROTORS

By using the more flexible definition of a motor proposed above, it is possible to recognize systems that make use of brownian motion and changes in chemical equilibrium as molecular machines. It is important to realize however, that although it is often expedient in understanding nanomachines and nanomotors to make direct analogies to macroscopic machines, in answering fundamental questions regarding problems associated with friction, wear, transmission, efficiency, fuel, motion and work, such facile comparisons often serve to cloud rather than simplify issues, and hence must be made with caution.

When considering a molecular motor and its operation, it should be noted that the forces that control the movement of macroscopic objects — in particular gravity — have little relevance to molecular machines of nanodimensions. In the world of the molecular machine, brownian storms rage relentlessly, and although refuge from the random brownian motion in solution can be found by resting on surfaces, even there, a molecule must contend with often significant thermally driven motion. This is not all bad news, however, as molecular dynamics is central to the operation of a molecular motor, as exemplified by the many membrane-immobilized biological motor systems. To move in such a turbulent world the molecular machine must either exploit brownian motion — as in brownian ratchets (see below) — or overcome it.

In designing motors²⁵ at the molecular level, random thermal brownian motion²⁶ must therefore be taken into consideration. Indeed, nature uses the concept of the brownian ratchet to excellent effect in the action of linear and rotary protein motors²⁵. In contrast to ordinary motors, in which energy input induces motion, biological motors use energy to restrain brownian motion selectively²⁷. In a brownian ratchet system the random-molecular-level motion is harnessed to achieve net directional movement, and crucially the resulting biased change in the system is not

reversed but progresses in a linear or rotary fashion. The problems associated with random thermal motion of molecules have been emphasized in discussions of ratchet-type motors (“if you can’t beat the chaos why not exploit it”²⁵) and nanomachines (“navigators on the nanoscale have to accommodate to the brownian storms”²⁸). It is in this direction that several groups have approached the challenge of controlling motion in molecular ratchets based on rotaxanes and catenanes^{29,30}.

Molecular rotor systems that embrace thermal brownian motion are ubiquitous. Numerous groups have focused on designing systems to understand molecular motion at the molecular and submolecular level in so-called technomimetic³¹ rotors (Fig. 2)^{32–37}. It is important to note, however, that these systems do not allow for directional control of movement. The dynamic processes observed for molecular rotor systems in solution, on surfaces and in the solid state are the subject of a recent comprehensive review and will not be discussed in depth here^{38,39}.

Although the majority of studies described have focused on molecular systems in solution, recent reports on crystalline molecular rotors^{32,33} (Fig. 2a) have addressed pertinent questions with regard to speed, friction and potential wear in a non-fluidic environment. Not only is fast free rotation in the solid state observed, but it was shown that, by careful consideration of the nature of the stator units and the molecular packing in the crystal lattice, the barrier to rotation can be reduced to near negligible levels. For instance, rotary motion around a carbon–carbon single bond can be extremely fast (up to 100 MHz), albeit with no control over the directionality of the rotation³³. It is worth remembering that molecular machines and molecules in general are not rigid, but undergo changes in their shape incessantly. From these studies it is clear that the dynamics within molecules and molecular flexibility are crucial factors to take into account in the design of artificial systems³⁵.

Although the direction of the motion in these systems is random, important design features demonstrate how control over rotary motion might be realized. For example, in the carborane rotors³⁶ shown in Fig. 2b, it has been suggested that unidirectionality of rotation might be achieved by the introduction of additional asymmetry using bulky groups. Despite these advances, brownian motion presents a tremendous challenge to the construction of molecular machines. Approaches can be taken to overcome the brownian turbulence, such as immobilization of molecular machines in membranes and on surfaces (see below) and construction of machines large enough to overcome brownian motion.

BETWEEN BROWNIAN AND NEWTONIAN MOTION

With the latter approach, to be able to build larger synthetic machines, the question arises as to how large the machines need to be. Where does the boundary between the domination of macroscopic ‘controllable’ newtonian motion and random brownian motion lie? The recent work of Whitesides⁴⁰, Sen^{41,42}, Ozin, Manners⁴³, and co-workers, although based on non-molecular systems, provides some insight. In their multimetallic systems, a combination of a metal capable of catalysing the decomposition of hydrogen peroxide (the chemical fuel) and a relatively inert metal allow for the generation of a local oxygen gradient and/or (difference in) surface tension, which provides the stimulus to move the metallic object with limited directional control (Fig. 3).

It is clear that the size of the object is critical to both the mechanism by which movement is induced and the extent of non-brownian motion involved⁴². For objects >50 µm in size, the movement induced by oxygen evolution is related to the physical effect of bubble

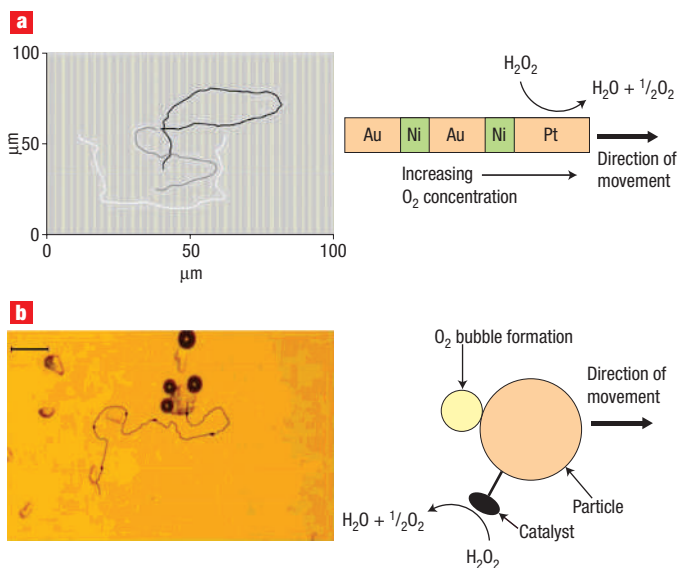


Figure 3 Chemically fuelled autonomously moving objects. The fuel applied is hydrogen peroxide. The propulsion is attributed to the decomposition of H_2O_2 to H_2O and O_2 creating a local oxygen concentration gradient and/or a difference in surface tension leading to translational movement. **a**, A striped Pt/Ni/Au/Ni/Au nanorod and the trajectory path of a nanorod spelling the letters ‘PSU’ in 5 wt% aq. H_2O_2 . Reproduced with permission from ref. 42. Copyright (2005) Wiley. **b**, Design of an autonomous moving microparticle and the trajectory followed by the particle on H_2O_2 decomposition (the black spots indicate O_2 bubble formation). In this system a molecular catalyst is anchored to an 80 µm silica particle. Note the difference in the mechanism for movement in these systems (oxygen gradients/surface tension or pressure from bubble formation). Figure reproduced from ref. 45 by permission of The Royal Society of Chemistry.

formation, whereas for particles <1 µm in size, the motion of the particles is indistinguishable from the inherent brownian motion of the system. Between 1 and 20 µm, however, movement is driven neither by brownian motion nor bubble formation but rather by oxygen concentration gradients⁴¹ in a manner proposed to be similar to that used by some bacteria⁴⁴. Achieving directional control in these systems is difficult but not impossible. It was demonstrated that the directionality can be controlled magnetically by using platinum–nickel–gold rods, in which platinum acts to create the oxygen gradient (that is, uses the fuel to generate propulsion, Fig. 3a) whereas the anisotropy of a magnetic nickel layer allows for control of the direction of the movement⁴².

Extension of this approach to molecular systems capable of chemically fuelled autonomous movement has been demonstrated recently, in our group, through the use of a synthetic catalyst that can effect efficient hydrogen peroxide decomposition (Fig. 3b)⁴⁵. Despite the fact that control over directionality of the translational movement is limited thus far, this latter molecular system demonstrates that the conversion of chemical to kinetic energy, and thereby movement of a micro-object, with the concerted action of molecular-scale motors is feasible.

Although in the previous example hydrogen peroxide was used as the chemical fuel to effect motion, in molecular systems, powering motion can be achieved by other chemical fuels, pH and redox changes and of course by light⁴⁶. Ideally the fuel used should not involve the generation of waste products, damage to the molecular machine and should allow for reversible external control, hence although chemically fuelled systems have been

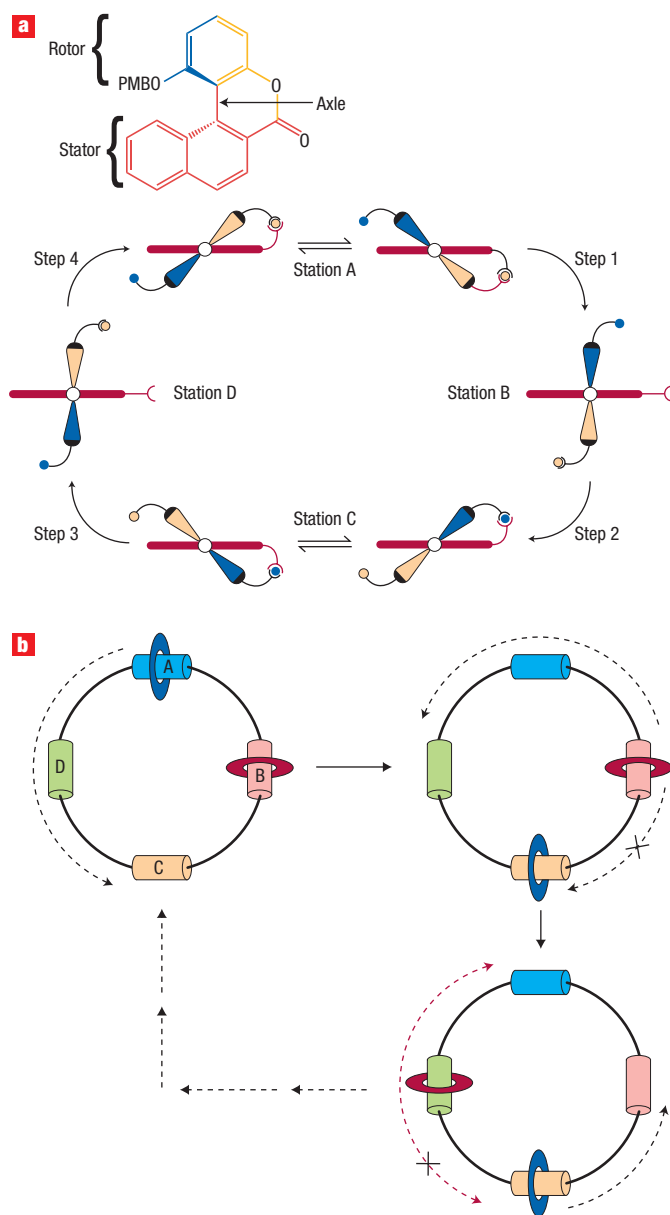


Figure 4 Rotary molecular motors in which a sequence of steps results in a full 360° unidirectional movement around the central axis. **a**, Molecular structure (station A) of a reversible, unidirectional molecular rotary motor driven by chemical energy and a schematic illustration of the rotary process. The bond-breaking processes rely on chiral non-racemic chemical fuel that discriminates between the two dynamically equilibrating helical forms, A and C. The bond-making processes between the rotor (yellow/blue) and the stator (red) use the principle that the sequential reactions are selective for either the blue or yellow parts of the rotor unit; that is, either the yellow or the blue end of the rotor can be selectively bound to the stator (red) to form A or C. Reprinted with permission from ref. 48. Copyright (2005) American Association of the Advancement of Science.

b, A four-station [3]catenane (a molecular assembly in which one or more rings are inter-locked) in which unidirectional movement along the ring is controlled by sequential chemical and photochemical reactions. Adapted with permission from ref 49. Part of the entire rotary process is shown; at each stage one ring blocks the reverse rotation of the other ring ensuring unidirectionality over the entire cycle.

demonstrated, the major focus in recent years has been on molecular machines fuelled photo- and/or electrochemically.

In the following sections we will describe several recent examples of molecular machines that can achieve controlled use of fuel to effect motion, and highlight key examples of how some of these systems demonstrate that molecular (nanoscopic) motion can realize effective macroscopic work.

UNIDIRECTIONAL ROTARY MOLECULAR MOTORS

Biosystems frequently rely on ATP as their energy source¹, however very few examples of artificial motors that use exothermic chemical reactions to power unidirectional rotary motion have been reported to date. To build synthetic molecular rotary motors, it is apparent that three criteria must be satisfied: (i) repetitive 360° rotation, (ii) consumption of energy and, of course, (iii) control over directionality.

Kelly and co-workers have achieved limited (120°) unidirectional rotation around a single carbon–carbon bond in a modified molecular ratchet using phosgene as the chemical fuel⁴⁷. Recently, our own group reported the unidirectional 360° rotation of a synthetic molecular motor fuelled entirely by a sequence of chemical conversions (Fig. 4a)⁴⁸. Importantly, the sense of rotary motion is governed by the choice of chemical reagents that control the rotor movement through four distinct stations. Within each station the rotor's brownian motion relative to the stator is restricted by structural features. Although the principle of a unidirectional rotary motor driven by a chemical fuel has been demonstrated, the requirement of a sequence of non-compatible chemical steps precludes continuous rotary motion with these systems thus far.

In a multicomponent approach to a combined chemically and photochemically driven unidirectional rotary motor, Leigh and co-workers have designed a complex [3]catenane-based molecular system comprising a large ring bearing four different stations and two smaller rings (Fig. 4b)⁴⁹. Sequential changes in position of the small rings along the four stations is achieved by applying light, chemical stimuli or heat, resulting in a unidirectional movement of the small rings along the larger one. In this process the backward brownian movement of one ring is prevented by the presence of the second ring. This system has also been engineered to make backward rotation possible by judicious choice of the components used⁵⁰.

By using light as fuel, however, continuous unidirectional rotary motion can be achieved. The photochemical step in these systems is the *cis* to *trans* isomerization of a carbon–carbon double bond (an alkene), which allows for a 180° rotation of one part of the molecule relative to another (Fig. 5a). This isomerization results in the movement of bulky groups into unstable positions, which relax thermally. The first generation of a light-driven unidirectional rotary motor⁵¹ comprises a central alkene unit that functions as the axis of rotation, and a chiral helical structure (Fig. 5b). The orientation of the methyl (Me) group determines the most stable shape that the molecule prefers to adopt and hence dictates if clockwise or anticlockwise rotary motion of one half of the molecule (the propeller) with respect to the other (the stator) occurs. By applying light and heat, unidirectional rotation proceeds as a sequential four-step process. The first generation of this approach to a molecular motor was extended in the second-generation motors, where the stator and rotor parts are quite different in molecular structure⁵², enabling additional components to be attached to either the top or the bottom half⁵³ and surface attachment of the stator (Fig. 5c)⁵⁴.

In order to apply these molecular motors, however, rotation at an appreciable speed — that is, 360° rotations per second — is desirable, if not essential. The structure of the second-generation motor is perfectly amenable to a whole range of structural modifications, which allow for fine tuning of the motor's properties, both photochemical and thermal. The speed of the photochemical step (*cis*–*trans* isomerization, Fig. 5) is of the

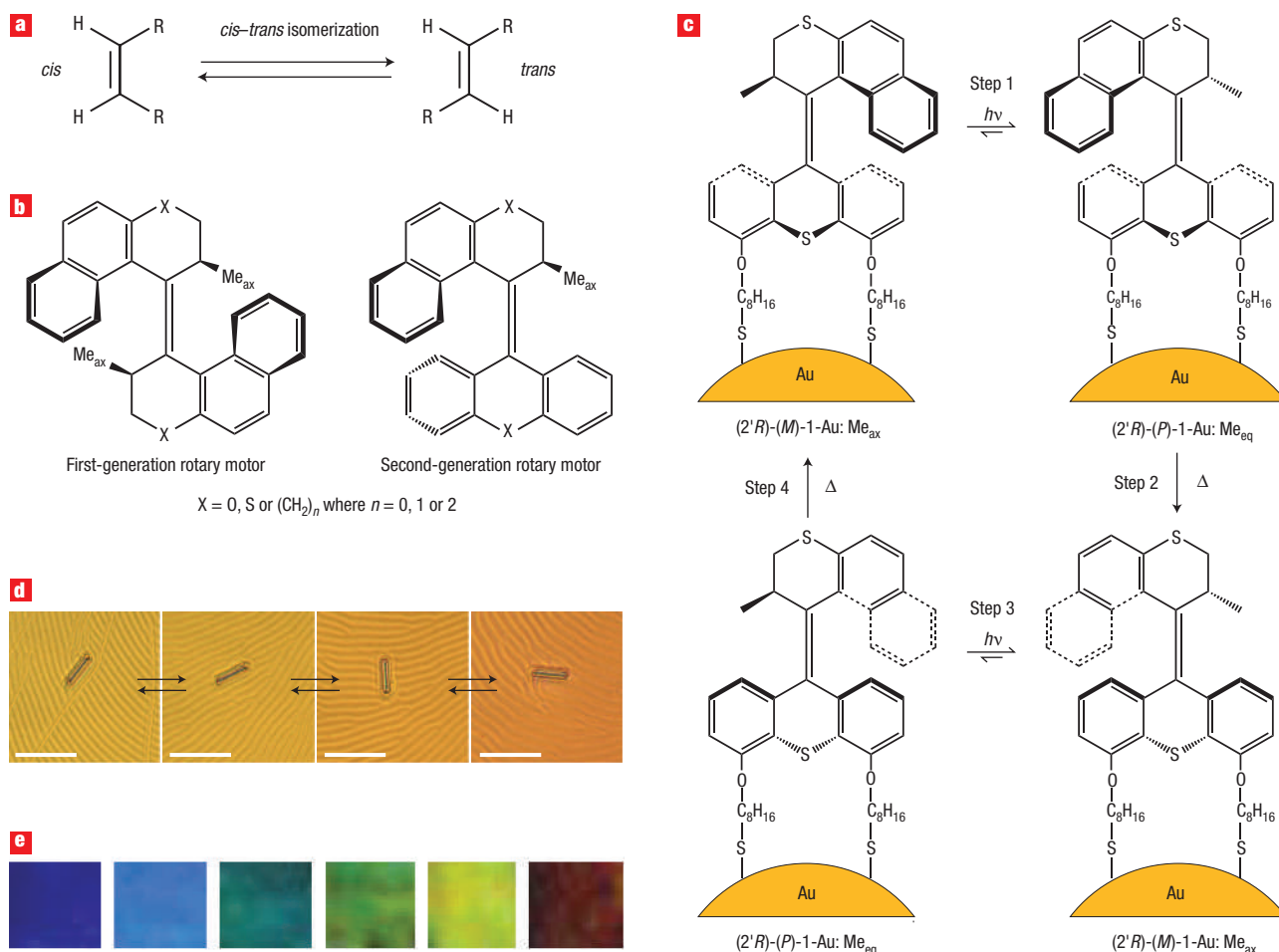


Figure 5 Light-driven unidirectional rotary motors in action. **a**, Principle of *cis-trans* isomerization around a double bond connecting two groups (R). Light absorption induces a rotary motion around the double bond, which results in a change in the relative position of the two R groups. **b**, Examples of first- and second-generation rotary motors that operate by photochemical *cis-trans* isomerization (Me_{ax} and Me_{eq} indicate axial and equatorial orientations of the methyl groups, respectively). **c**, Second-generation rotary motor immobilized on a gold surface. The first photochemical *trans-to-cis* isomerization forces the molecule into a highly strained *cis*-geometry. Rotary motion continues in the same direction as the consequence of a thermal helix inversion that results in a release of the strain in the molecule. Subsequent irradiation induces a *cis-to-trans* isomerization, which is followed by a second thermal helix inversion, again with release of conformational strain, to provide the initial state. Reproduced with permission from ref. 54. **d**, Glass rod rotating on a liquid crystal, doped with a second-generation light-driven molecular motor, during irradiation with ultraviolet light. Frames were taken at 15 s intervals and show clockwise rotations of 28° (frame 2), 141° (frame 3) and 226° (frame 4) of the rod relative to the position in frame 1. Scale bars, 50 μm . Note that heating was not involved as the thermal isomerization was efficient at room temperature. Reproduced with permission from ref. 101. **e**, Example of colour changes observed in motor-doped liquid crystals on irradiation. Liquid-crystal phase: E7(Merck) 6.16 wt% doping. Reproduced with permission from ref. 102. Copyright (2002) National Academy of Sciences, USA.

order of 1 or 2 ps (ref. 55). Hence the rate of rotation is controlled by the thermally induced relaxation of the unstable to the stable state, which requires bulky groups (for example, the methyl and phenyl rings) to pass each other. Structural modification of the bridging atoms and substituents allows for reduction of the energy barrier of the thermal steps, which has led to a 1.2-million-fold increase in the rotation speeds achievable with the second-generation motors⁵⁶. These improved motors allow the propeller to rotate unidirectionally on irradiation at up to 80 revolutions per second at 20 $^\circ\text{C}$.

LINEAR MOLECULAR MOTORS

Rotaxane-based systems have dominated the field of artificial molecular machines designed to achieve translational motion^{20,57}.

Typically, such systems contain a ring component that shuttles reversibly between stations on the shaft (Fig. 6) with the movement controlled by redox chemistry^{58–60}, pH changes⁶¹ or light⁶².

The development of increasingly sophisticated photochemically active rotaxanes has culminated recently in linear motors powered by light⁶³, which allow for movement of a shuttle up to 1.5 nm with a frequency of 10 kHz. These systems operate with a quantum efficiency of up to 20%. Translating the light-driven motion in these molecules into useful work remains a challenge⁶⁴, however, the recent development by Balzani, Stoddart and co-workers⁶⁵ of an autonomous photo-driven rotaxane is a significant step forward in achieving this goal.

A design for an artificial molecular muscle based on the sliding motions of the ring along the shaft of rotaxanes was also reported⁶⁶. Two interlocked rotaxanes allow for elongation and contraction

by binding different metal ions, a system reminiscent of the Ca^{2+} -driven processes that occur during muscle contraction. An example of a chemically driven system designed to mimic processive enzymes⁶⁷ has been reported recently⁶⁸ and is a significant step in the development of synthetic processive molecular machines akin to those found in nature⁶⁷.

MULTICOMPONENT MECHANICAL MACHINES

The construction of molecular machines, in which mechanical motion of different units operate in concert, for example when rotary motion of one part is coupled to linear motion of another part, requires the design of integrated multicomponent systems. A system denoted as a 'molecular elevator' composed of three rotaxane units interlocked mechanically to a platform was reported recently (Fig. 7a)^{69,70}. The charge of one of the two stations is sensitive to pH changes and as a result the platform can move between two levels by adding acid or base.

Although large changes in physical properties can be brought about using *cis-trans* isomerization, the direct conversion of light energy into 'mechanical work', that is, significant motion, is a more challenging goal. Following an earlier design of molecular scissors⁷¹, the coupling of several molecular motions was achieved in a light-powered 'molecular pedal'⁷². A change in molecular shape on *cis-trans* photoisomerization of an azobenzene unit is transmitted via a pivot point (a ferrocene unit) and a pedal-like motion of large flat zinc porphyrin units to induce a clockwise or anticlockwise rotary motion in a bound rotor guest. This system demonstrates that small changes in molecular structure can be used to drive much larger mechanical changes, remote from the point of initial mechanical motion.

Recently, the light-driven molecular motors, shown in Fig. 5, were used by Tour and co-workers to construct a prototype light-powered "nanocar"⁷³. In this approach carborane 'wheels' were attached covalently to a molecular rotor 'engine' (Fig. 7b). Although this multicomponent system did not compromise the functionality of the motor unit itself, light-driven movement across a surface awaits demonstration.

MOTORS ON SURFACES

The molecular motors discussed above that convert chemical or light energy into directional rotary or linear motion all operate in solution, and although brownian motion can be overcome by building micrometre-dimension devices, another approach to overcoming brownian motion and bringing about order is to immobilize machines on a surface. However for nanomachines to be able to operate in devices or to perform useful work it will be essential that the motors do not lose functionality when immobilized. Anchoring and subsequently addressing molecular machines on surfaces is critical to the successful interfacing of nanomechanical systems with the macroscopic world.

Altitudinal molecular rotors (the rotor axle is parallel to the surface), which exhibit a strong dipole moment, have been immobilized on Au(111) surfaces⁷⁴. Barrier-height imaging using scanning tunnelling microscopy measurements revealed that the direction of the dipole of the rotor unit turns in response to a static electric field imposed by the tip of the microscope. On the basis of molecular dynamics calculations, it was suggested that limited directionality in their motion should be possible using oscillating electrical fields normal to the surface⁷⁵. A similar approach has been reported very recently by Miyake and co-workers⁷⁶ using lanthanide complexes, in which the large metal ion is sandwiched between two flat porphyrins, the speed of rotation of which can be modified by varying the lanthanide metal used⁷⁷.

The second-generation light-driven unidirectional molecular rotors discussed above (Fig. 5c) have been immobilized successfully on nanoparticle gold surfaces to yield an azimuthal (rotor axle normal to the surface) motor. In these systems the stator component carries two thiol-functionalized 'legs' that connect the entire motor to the surface⁵⁴. Repetitive and unidirectional 360° rotary motion with respect to a surface was observed to occur on irradiation. The use of two attachment points per molecule prevents uncontrolled thermal rotation of the entire motor system with respect to the surface. However, this study also demonstrates the difficulties that may be encountered in such immobilization⁵⁴. The length and nature of the connecting units (legs) is frequently a critical issue in the attachment of photoactive compounds to metal surfaces as it can affect excited-state processes dramatically⁷⁸.

The tetrathiafulvene unit has proven to be a mainstay in the design of electrochemically driven rotaxane-based molecular machines, as it can be converted between two stable states (bistable), that is, the neutral and oxidized forms, which show markedly different behaviour when interacting with other molecular components⁷⁹. Analogous to *cis-trans* isomerization, facile reversible oxidation to the mono- or dicationic states of the tetrathiafulvene unit can be used to effect large changes in the position of rings along the shaft unit of rotaxanes⁸⁰. These redox-switchable 'bistable' rotaxanes have been applied as monolayers in molecular switch tunnel junction devices^{81,82}. Importantly, the position of the shuttle can be controlled by either reduction or oxidation but the conductance of the system is measured only as a function of the position of the shuttle on the rotaxane. In contrast to more conventional approaches to redox-switchable systems where a change in redox state is used to control conductivity, in this example the redox changes are used to move a molecular component only.

Whereas demonstration of linear and rotary motion on the nanometre scale is apparent in the synthetic molecular machines described above, realizing the summation of motion at the molecular level to achieve macroscopic motion, for instance mimicking the operation of myosin/actin-driven movement of muscles, is more challenging⁸³. Nevertheless, it has been demonstrated that such translation of work can be achieved^{84,85}. The approaches taken include: (i) changes in molecular properties such as surface tension, (ii) indirect macroscopic movement through amplification of molecular motion and (iii) direct translation of molecular to macroscopic motion.

MOLECULAR MOTORS AT WORK

In the individual steps of the artificial molecular motors constructed so far, the system acts as a mechanical switch. Molecular switches have found widespread application in the dynamic control of bulk materials and single-molecule properties, as well as molecular devices that take advantage of the ability to trigger functions through external signals²¹. Molecular switches can be used to modulate properties such as surface wettability⁸⁶, polymer elasticity⁸⁷, lateral pressure profile of bilayers⁸⁸, host-guest recognition⁸⁹, supramolecular organization⁹⁰, catalysis⁹¹, colour⁹², fluorescence⁹³, conductance⁹⁴ and enzyme activity⁹⁵⁻⁹⁷. The use of photochemical molecular switches has the advantage of short response times, clean and tuneable energy input, and the ability to convert an optical input into a variety of useful output signals.

It is therefore unsurprising that indirect translation of changes in molecular properties to achieve macroscopic movement has used the reversible photochemical switching of bistable molecules, such as azobenzenes, mounted on surfaces^{98,99}. Photochemical

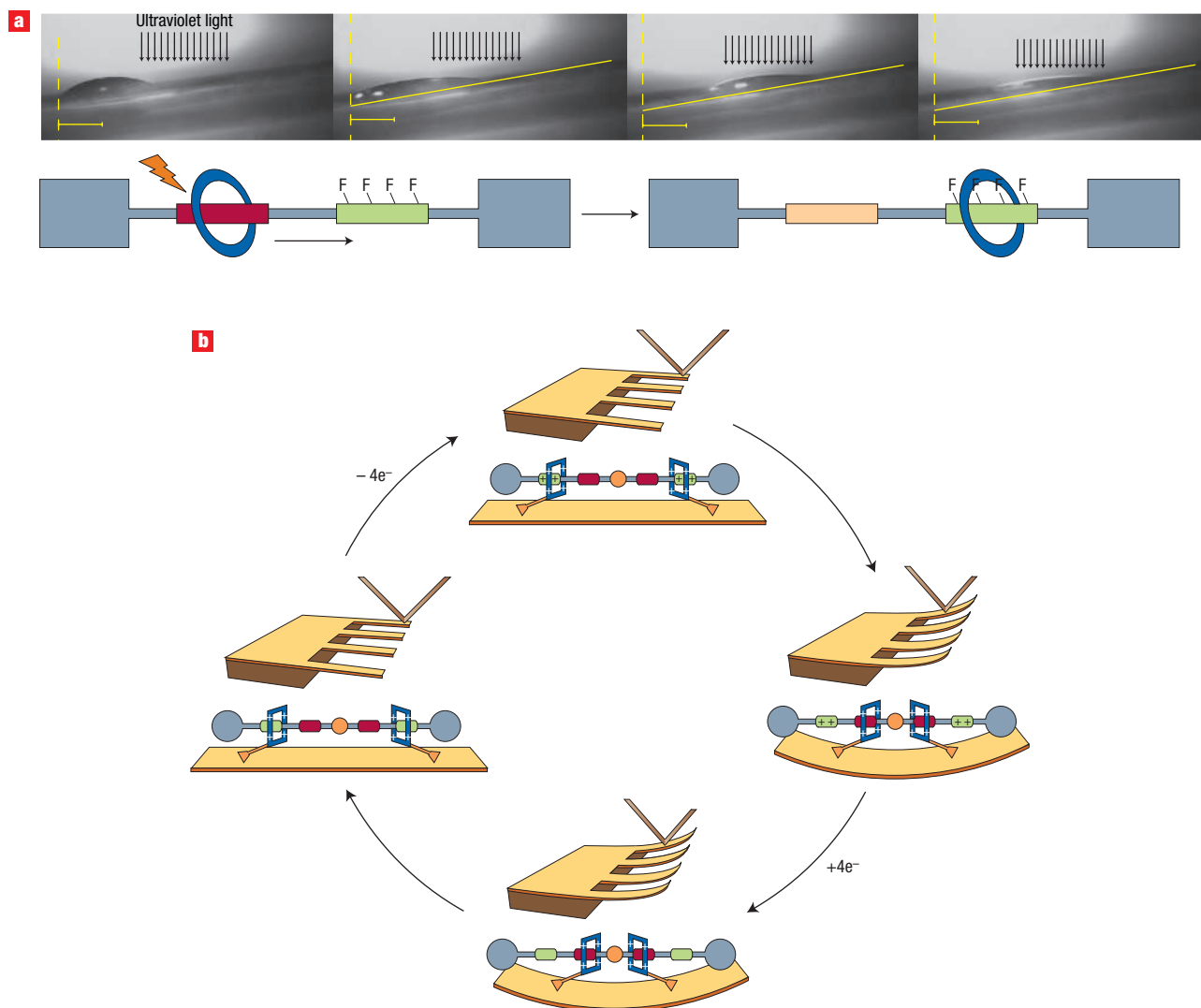


Figure 6 Synthetic molecular systems designed to achieve translational motion. These linear molecular motors are so-called rotaxanes in which one (or more) rings can move from one binding site to another along a shaft. The change in equilibrium position is triggered by an external signal. **a**, Macroscopic transport of liquids by surface-bound rotaxanes as a synthetic molecular machine. The position of the ring exposes or conceals a fluoroalkane component and concomitantly changes the surface energy. The ring is moved by shining light on the surface coated with motor molecules. When the area above the droplet of liquid is 'switched', the liquid is attracted to the irradiated zone, and in this way is transported across the surface and, in this case, up a slope (with 12° incline). Scale bars = 100 μm. Reproduced with permission from ref. 101. **b**, Design of a molecular muscle and the bending of cantilever beams by the cooperative action of several linear rotaxane motors. The system is based on a bistable [3]rotaxane structure involving a rotaxane with two positively charged rings and four stations, two of which are redox active units and can be switched between a neutral and positively charged form. The rings are connected to the surface of the cantilever via disulphide containing tethers to form a self-assembled monolayer. The rings are initially sitting on the redox-active stations in their neutral state (structure on the left). Oxidation of the redox-active stations, forces the rings to move to the inner neutral stations and results in contraction of the rotaxane, bending the beam. Adapted with permission from ref. 85. Copyright (2005) American Chemical Society.

isomerization of azobenzenes attached to surfaces was used to induce wetting/dewetting by changing the surface energy of the monolayers and allowing for the transport of liquid droplets across surfaces¹⁰⁰. Similar millimetre-scale directional transport of droplets on a surface with light was achieved with a photoactive rotaxane operating as a linear nanomechanical switch (Fig. 6a)¹⁰¹. The system comprises a shuttle (the ring that moves along the shaft) on a thread with a fluoroalkane station and a photo-responsive fumaramide station, which has a high binding affinity for the shuttle. The entire system was anchored through physisorption on a modified gold surface.

Photochemical *trans-cis* isomerization of a fumaramide unit in the thread reduces the binding affinity to the shuttle drastically and, as a consequence, the equilibrium position of the shuttle changes in favour of the fluoroalkane station. The shuttle movement is therefore used to expose or conceal the fluoroalkane part, which results in a change in surface energy and, as a consequence, the movement of liquid. The collective action of a monolayer of these molecular shuttles makes them operate as a motor and has sufficient power to move a microlitre droplet of diiodomethane on a millimetre scale up a 12° incline (Fig. 6a).

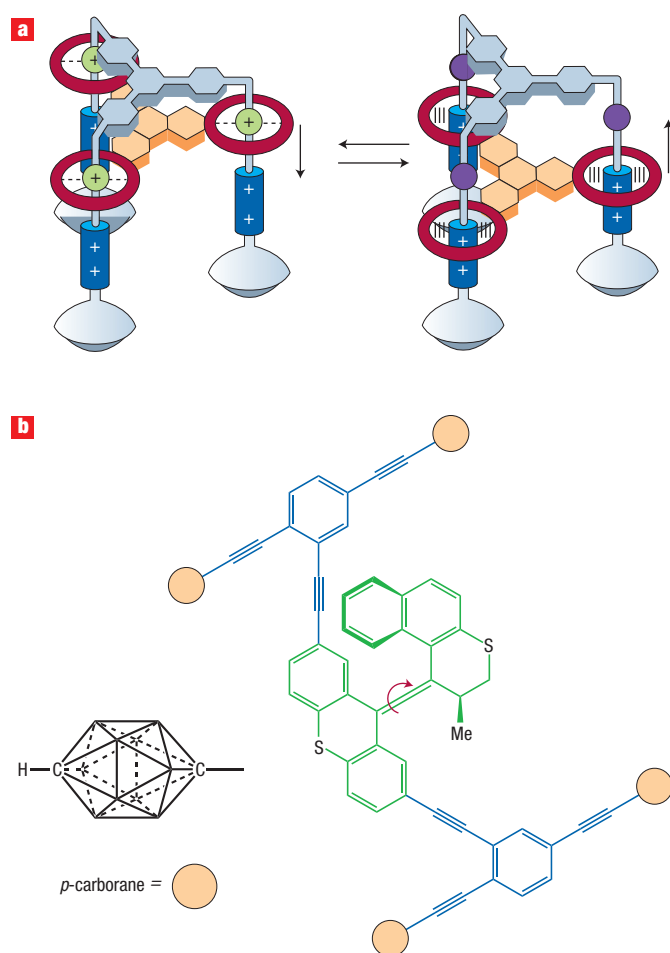


Figure 7 Systems designed as multicomponent mechanical machines. **a**, A multicomponent rotaxane that operates as a molecular elevator. A platform is connected to three rotaxane units. Acid–base controlled switching in all three rotaxane units results in movement of the position of the platform relative to the rotaxane legs. Adapted with permission from ref. 70. Copyright (2006) American Chemical Society. **b**, Prototype for a light-driven molecular car. Four carborane ‘wheels’ are connected to a molecular frame that incorporates a light driven molecular motor. The linear molecular rods connecting the wheels act as axles and the central rotary motor component is incorporated to move the molecular car forward, by ‘paddling’⁷³.

Although changes in molecular structure can be used to effect large changes in macroscopic properties, indirect macroscopic movement induced by changes in molecular chirality was demonstrated only recently. The reversible rotation of surface textures and microscale objects can be achieved using specially designed second-generation light-driven rotary molecular motors embedded in a liquid-crystal film (Fig. 5d)¹⁰². This motor has a right-handed helical structure and is very effective at inducing dynamic helical organization when applied as a chiral dopant in a liquid-crystalline film. The energy provided by light (the fuel for the motor) does not effect movement of a macroscopic object by itself. However, change in chirality of the motor is amplified through the liquid-crystalline host matrix. The result is a reorganization of the polygonal texture of the film in a clockwise or anticlockwise rotational fashion following the photochemical or thermal isomerization steps of the motor molecule. The rotation of the motor used as a dopant is ‘transmitted’ to the surface through the

reorganization of the liquid crystal. A surface relief of 20 nm was observed by non-contact atomic force microscopy. The orientation of the surface relief alters in response to the topology change in the embedded molecular motor. This reorganization generates a torque sufficient to achieve unidirectional rotation of microscopic objects placed on top of the film. These experiments show that a molecular motor can actually perform work. By harvesting light-energy and the collective action of molecular motors, microscopic objects that exceed the nanomotor in size by a factor of 10,000 can be rotated, with directional control.

The application of synthetic molecular motors in liquid-crystalline systems is not limited to the movement of objects. The change in handedness of the motor molecule during the rotary steps induces a reorganization of the liquid-crystalline film and induces a reversible and, importantly, tuneable change in the colour of the film (Fig. 5e)¹⁰³. Therefore the macroscopic properties of a material can also be changed using a molecular rotary motor, and in this specific case, pixel generation with colours covering the entire visible spectrum is achieved readily.

Concerted macroscopic motion induced by changes in molecular structure is the fundamental basis of muscular movement. Hence, the possibility of a direct translation of molecular motion to macroscopic levels is, of course, an important goal. The molecular muscle developed by Stoddart and co-workers is based on linear molecular motors and uses a bistable [3]-rotaxane structure with two rings and four stations (Fig. 6b)^{84,85}. Tethers attached to each ring anchor the whole rotaxane system as a self-assembled monolayer to the gold surface of microcantilever beams. The array of cantilever beams, decorated with these rotaxane molecules, shows reversible bending through sequential addition of chemical oxidants or reductants. The redox chemistry that drives the process is possible because of the presence of the redox-active units at two of the four stations. Redox-switching of the redox-active units initiates a change in the equilibrium position of the positively charged rings on the rod of the rotaxane, driven by a change in electrostatic repulsion. This change in inter-ring distance induces a change in mechanical stress on one side of the microcantilever. The combined effect of a monolayer of these bistable units operating collectively on a surface is to induce a bending of the cantilever. This demonstrates that controlled molecular motion in a wholly synthetic system can effect macroscopic movement.

In the systems developed by Gaub^{104,105} Broer¹⁰⁶ and co-workers, photochromic azobenzenes have been used as tools to generate large reversible anisotropic changes in linear and stiff crosslinked polymer networks, respectively. The simplicity of these systems and the reversibility of the changes on irradiation with different wavelengths of light holds considerable potential for the future development of molecular-based polymer actuator materials.

MOLECULAR VALVES

That biological motors perform work and are engaged in well-defined mechanical tasks such as muscle contraction or the transport of objects is apparent in all living systems. Controlling motion using molecular switches is particularly attractive for the construction of nanomechanical valves¹⁰⁷. For instance, the affinity of crown-ether type receptors to bind cations can be modulated reversibly by light when azobenzene photo-switches are incorporated in these receptors⁸⁹.

A light-actuated nanovalve derived from a channel protein was constructed in our group to control photochemical transport of solutes across a lipid bilayer. The valve consists of a channel protein modified with a photochemical active spiropyran switch¹⁰⁸. The reversible molecular photochemical switch acts as a valve control

for the 3 nm channel (Fig. 8a). The valve can be opened and closed with ultraviolet and visible light, respectively. This is possible because the neutral switch molecule converts to its highly polar zwitterionic form on irradiation with ultraviolet light. The hybrid protein valve is compatible with a liposome encapsulation system and allows for external photo-control of transport through the channel, demonstrated in the controlled release of an encapsulated fluorescent compound.

A different approach to photochemical valve control involves a bio-hybrid system in which movement through a channel is controlled allosterically¹⁰⁹. A semisynthetic ligand-gated ion channel that can be turned on and off by ultraviolet and visible light irradiation, has been developed using an azobenzene (Fig. 1) optical switch (Fig. 8b). The azobenzene switch is attached both to the protein and the glutamate residue, which is specific for the allosteric site (a signal binding site on the protein, which regulates the operation of a separate remote functional component) responsible for closing the protein channel. The point of attachment is naturally critical to its operation, and in contrast to the previous example, the switching unit is attached to the outside of the channel rather than the inside. *Trans*-to-*cis* photoisomerization of the azobenzene unit results in a large geometric change in the molecule and, as a consequence, glutamate binds to the receptor and the channel opens. In this nanomechanical valve, several structural units and functions operate in concert to allow reversible channel gating controlled by light.

Redox processes offer an attractive alternative to light-controlled nanomechanical valves because of the possibility of integration into nano-electronic devices. A quite simple yet elegant example of such a molecular valve is based on cyclophanes (large molecular rings), where oxidation can be used to open and reduction to re-close a cavity¹¹⁰. Although the channel itself is very small when compared with the protein-based systems described above, this system does hold potential for the development of fully synthetic molecular valves.

An alternative approach to redox-controllable reversible nanovalves is found in a rotaxane-based valve system¹¹¹. The principle involves reversible blocking of solid pores, which allows controlled release of fluorescent dyes from mesoporous (pore size 1.5–2.0 nm) silica particles.

The construction of functioning nanovalves, with movable molecular control units to regulate flow of substances, is a significant step towards the development of real nanomachines. Such nanovalves are, however, attractive components in themselves, for use in drug delivery systems with controlled release, signal transduction, sensors and nanofluidic systems, for example.

CONCLUSIONS AND OUTLOOK

The exquisite solutions nature has found to control molecular motion, evident in the fascinating biological linear and rotary motors, has served as a major source of inspiration for scientists to conceptualize, design and build — using a bottom-up approach — entirely synthetic molecular machines. The desire, ultimately, to construct and control molecular machines, fuels one of the great endeavours of contemporary science. The first primitive artificial molecular motors have been constructed and it has been demonstrated that energy consumption can be used to induce controlled and unidirectional motion. Linear and rotary molecular motors have been anchored to surfaces without loss of function — a significant step towards future nanomachines and devices. Furthermore, it has been demonstrated unequivocally that both linear and rotary motors can perform work and can

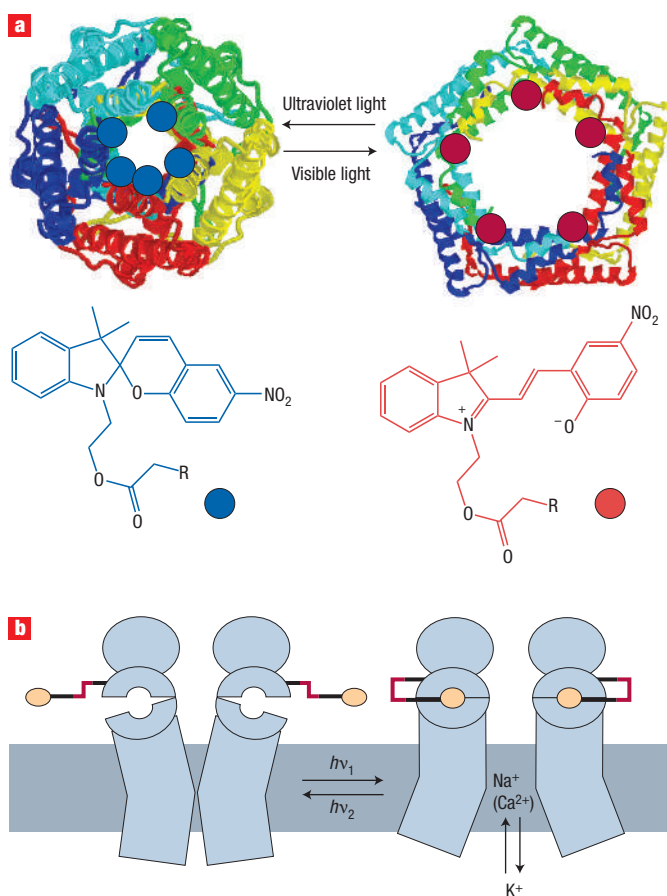


Figure 8 Two approaches to the opening and closing of nanovalves using molecular switches. **a**, A light-actuated nanovalve based on a mechano-sensitive channel protein modified with spiropyran photoswitches¹⁰⁸. When ultraviolet light is shone on the protein, the molecular switch is converted from its neutral, hydrophobic, form to a charged polar form. The change in hydrophobicity in the channel results in the channel opening. Visible light reverses the process and closes the channel again. **b**, Photochemical allosteric control of a glutamate-sensitive protein channel based on the azobenzene molecular switch. In this example, the switching unit is not incorporated in the channel itself but instead is located on the outside of the channel protein. When light is shone on the azobenzene switch (see Fig. 1), the glutamate is brought into contact with a receptor site on the outside of the protein. The binding of glutamate to this site results in opening of the protein valve. Again, the process is reversed by shining light of a different colour on the protein, which moves the glutamate away from the control site. Reproduced with permission from ref. 109.

move objects. However, although the first applications of molecular motors to the control of other functions have been realized, the whole field is still very much in its infancy and offers ample opportunity in the design of nanomechanical devices.

Major challenges in the development of useful nanomachines remain, such as the development of fast and repetitive movement over longer time frames, directional movement along specified trajectories, integration of fully functional molecular motors in nanomachines and devices, catalytic molecular motors, systems that can transport cargo and so on. As complexity increases in these dynamic nanosystems, mastery of structure, function and communication across the traditional scientific boundaries will prove essential and indeed will serve to stimulate many areas of

the synthetic, analytical and physical sciences. In view of the wide range of functions that biological motors play in nature and the role that macroscopic motors and machines play in daily life, the current limitation to the development and application of synthetic molecular machines and motors is perhaps only the imagination of the nanomotorists themselves.

doi:10.1038/nnano.2006.45

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Acknowledgements

The Authors thank M. M. Pollard for many suggestions and reading of the manuscript.